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Ethnic Prevalence of Angiotensin-Converting Enzyme Deletion (D) Polymorphism and COVID-19 Risk: Rationale for Use of Angiotensin-Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers

血管紧张素I转化酶缺失(D)的种族患病率多态性与COVID-19风险: 血管紧张素I转化酶抑制剂/血管紧张素受体阻滞剂使用原理阐述

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Abstract 摘要

Rationale 原理阐述

Hypertension, obesity and diabetes are major risk factors associated with morbidities underlying COVID-19 infections. Regression analysis correlated presence of ACE insertion/ deletion (I/D) polymorphism to COVID-19 incidence and mortality. Furthermore, COVID-19 prevalence correlated to allele frequency of angiotensin-converting enzyme (ACE) deletion (D) polymorphism within the European population.

高血压、肥胖和糖尿病是潜在COVID–19感染相关的主要危险因素。血管紧张素转换酶(ACE)插入/缺失(I/D)多态性与COVID–19发病率和死亡率的相关性回归分析。此外，在欧洲人群中，COVID–19的流行与血管紧张素 I 转化酶(ACE)缺失(D)多态性的等位基因频率有关。

Objective 目的

Homozygous ACE deletion polymorphism is associated with increase in ACE and angiotensin II (Ang-II), sustained levels can result in inflammation, fibrosis and organ damage. The ACE DD polymorphism is also associated with hypertension, acute respiratory distress and diabetic nephropathy, all considered high risk for COVID-19 infection and outcomes. The study objective was to describe a biological framework associating ethnic prevalence of ACE deletion polymorphism to COVID-19 comorbidities providing rationale for therapeutic utility of ACE-I/ ARBSs to improve outcomes.

纯合ACE 缺失多态性与血管紧张素转换酶和血管紧张素 II (Ang–II，下文用Ang–II替代)的增加相关，持续的高水准可导致炎症、纤维化和器官损伤。ACE DD 基因多态性还与高血压、急性呼吸窘迫和糖尿病肾病有关，这些疾病都被认为是COVID–19疾病感染和预后的高危因素。这项研究的目的是描述一个生物学框架，就是将 ACE 缺失多态性的种族患病率与COVID–19合并症相联系，为ACE–I/ARBSs 的治疗效果改善预后提供理论依据。

Method and Results 方法和结果

The Allele Frequency Database (ALFRED) was queried for frequency of rs4646994 representing ACE I/D polymorphism. In a total of 349 worldwide population samples, frequency of ACE D allele was higher in European, Asian, and Africans cohorts. In the USA, the frequency of ACE D allele was higher in non-Hispanic Black compared with non-Hispanic White and Mexican Americans.

等位基因频率资料库(ALFRED)中查询表示ACE I/D多态性的rs4646994的频率。在来自全球349个人口样本中，ACE D等位基因的频率在欧洲、亚洲和非洲人群中较高。在美国，ACE D等位基因在非西班牙裔黑人中出现的频率高于非西班牙裔白人和墨西哥裔美国人。

Conclusion 结论

COVID-19 binding mediated reduction/inactivation of ACE-II can increase ACE/Ang-II signalling pathway and related pathologies. The presence of ACE DD polymorphism with COVID-19 infection likely augments ACE/Ang-II activities, increasing severity of COVID-19 morbidities and impacts outcomes. Thus, ethnic prevalence of ACE DD polymorphism can explain in part the severity of COVID-19 morbidity providing rationale for the use of ACE-I/ARBSs to improve outcomes.

COVID-19结合介导的 ACE-II 减少/失活可增加 ACE/Ang-II 信号通路及相关病理。在COVID-19感染中存在ACE DD多态性可能增强ACE/Ang-II活性，增加COVID-19疾病的严重程度并影响预后。因此，ACE DD多态性的种族患病率可以部分解释COVID-19发病的严重程度，为使用ACE- I/ARBSs改善预后提供依据。

Introduction 引言

The SARS-CoV-19 (COVID-19) infection has infected in excess of seventeen million individuals around the globe and is designated as a pandemic by the World Health Organization. The global efforts are focused on understanding the disease onset, progression and to identify causal linkage for differences in observed outcomes among the affected population and within specific demographics. Despite worldwide spread of the COVID-19 infections, European countries and the USA appear to have experienced higher incidence and mortality rates [1,2,3]. Hypertension, obesity, and diabetes were identified as the most common comorbidities associated with COVID-19 infection; higher severity of disease and mortality was generally reported in the elderly (>50 years) population.

SARS-CoV-19 (COVID-19)感染了全球1700多万人，被世界卫生组织定为全球流行病。全球努力的重点是了解疾病的发病、进展，并确定受影响人口之间和特定人口统计数据中观察到的结果差异的因果联系。尽管COVID-19传染病在全球范围蔓延，但欧洲国家和美国的发病率和死亡率似乎较高[1,2,3]。高血压、肥胖和糖尿病被确定为与COVID-19感染相关最普遍合并症;老年人(> 50岁)的疾病严重程度和死亡率普遍较高。

Angiotensin-converting enzyme 2 (ACE2) is the predominant receptor for SARS-CoV viral entry and infection, resulting in the reduction of expression of ACE2 [4, 5]. ACE2 is an enzyme component of the renin-angiotensin system (RAS), a complex integrated network of peptides-enzyme combination, generating catalytically active peptides with prominent influence on the vascular, renal, cardiac, and immune system [6]. In this report, we describe a framework of the pathophysiological consequence of COVID-19-induced reduction in ACE2, i.e., overactivation of the RAS pathway with the potential to have deleterious effect on organ functions including the lungs, kidneys, heart, and immune system. The deleterious activities of RAS within the COVID-19-infected cohorts can be further amplified by the presence of genetic polymorphism in the angiotensin-converting enzyme (ACE). Increased prevalence in frequency of the ACE polymorphism within ethnic groups, in part, is likely responsible for the observed severity of COVID-19 comorbidities and mortality in this population. This is substantiated by recent regression analysis linking presence of ACE-1 I/D (insertion/deletion) polymorphism with incidence and mortality with COVID-19 infection [7].

血管紧张素转化酶2（ACE2）是 SARS–CoV 病毒进入和感染的主要受体，这导致 ACE2 [4, 5] 的表达减少。血管紧张素转换酶2是肾素–血管紧张素系统（RAS，下文均用RAS替代）的一个酶组分，该系统是一个由多肽–酶组合而成的复杂综合网路，能产生具有催化活性的多肽，从而对血管、肾脏、心脏和免疫系统产生显著影响[6]。在本报告中，我们描述了 COVID–19诱导 ACE2 减少的病理生理学结果的框架，即过度启动 RAS 通路，可能对器官功能包括肺、肾脏、心脏和免疫系统产生有害影响。在 COVID–19感染的同源群体中 RAS 的有害活性可以通过血管紧张素转化酶(ACE)基因的遗传多态性进一步放大。种族群体中 ACE 多态性频率的增加，在某种程度上可能是该人群中观察到的严重的COVID–19疾病合并症和死亡率的原因。最近美国回归分析学会将 ACE–1 I/D (插入/缺失)多态性的存在与COVID–19疾病感染的发病率和死亡率联系起来，证实了这一点[7]。

Renin-Angiotensin System: ACE, Ang-II, and Inflammation

腎素-血管緊張素系統（RAS): 血管緊張素轉化酶，血管緊張素-2(下文均用Ang-II替代），和炎症

The RAS system has a prominent role in the regulation of vascular dynamics; its components directly or indirectly influence functions of the lung, heart, kidney, brain and the immune system [6]. In addition to central RAS components, i.e., renin (kidney), ACE (lungs), and angiotensinogen (liver), tissue-specific localized systems including the kidney, heart, and lungs have been identified [6, 8]. Within RAS, the canonical angiotensin-converting enzyme (ACE) is responsible for conversion of angiotensin-1 (Ang-I) to angiotensin-2 (Ang-II) (Fig. 1a). Subsequently, Ang-II mediates its effects through activation of AT-1 and AT-2 receptors, resulting in distinct intracellular signalling pathways [9,10,11]. Activation of AT-1 receptors is associated with the well-characterized physiological actions of Ang-II in various organs including the lung, heart, kidney, and the vascular system [10].

RAS 系统在调节血管动力学方面有重要作用，其组成部分直接或间接地影响肺、心脏、肾脏、大脑和免疫系统的功能[6]。除了肾素(肾)、血管紧张素原(肺)和血管紧张素原(肝)等中枢 RAS 成分外，还发现了包括肾、心脏和肺在内的组织特异性局部系统[6, 8]。在 RAS 系统中，典型的血管紧张素转化酶(ACE)负责血管紧张素-1(Ang-I)转化为血管紧张素-2(Ang-II)(图1a)。随后，Ang-II 通

过启动 AT-1和 AT-2受体介导其作用，导致不同的细胞内信号通路[9,10,11]。AT-1受体的启动与 血管紧张素-2(Ang-II)在包括肺、心脏、肾脏和血管系统在内的各种器官中的生理作用有关[10]。

Fig. 1 (Full size image)

图一 （下载原尺寸图片）

a Overview of the renin-angiotensin system. The figure describes the basic components of the renin angiotensin system with focus on the impact of ACE and ACE2 in the generation of angiotensin peptides, the respective cognate receptor(s) and corresponding physiological consequence of receptor activation. **b** Influence of ACE deletion (DD) polymorphism on renin-angiotensin system. The figure describes the consequence of the ACE deletion polymorphism, the increase in levels of ACE and angiotensin II resulting in activation of AT-1 receptor and downstream pathophysiological effects. **c** Consequence of COVID-19 infection and ACE Deletion (DD) polymorphism on renin-angiotensin system. The figure describes the increased activation of ACE and generation of Ang-II as a consequence of COVID-19-mediated reduction in ACE2 in the presence of ACE deletion polymorphism. The result is disruption of physiological balance of the ACE/ACE2 axis resulting in overactivation of AT1-R signalling and associated pathological consequence

a. RAS系统概述。该图描述了RAS的基本组成，重点介绍了 ACE 和 ACE2在血管紧张素肽生成中的作用、各自的同源受体及受体启动的相应生理后果。b. ACE 缺失(DD)多态性对RAS。该图描述了 ACE 缺失多态性的后果，ACE 和Ang-II 水准的增加导致 AT-1受体的启动和下游病理生理效应。c. COVID-19疾病感染和 ACE 基因多态性对RAS的影响。该图描述了 ACE 启动增加和Ang-II 的产生是由于存在 ACE 缺失多态性 covid-19介导的 ACE2减少。其结果是 ACE/ACE2轴的生理平衡被破坏，导致 AT1-R 信号的过度启动和相关的病理后果

In addition to its hemodynamic effect, Ang-II has significant pro-inflammatory effects, promoting generation of reactive oxygen species (ROS), cell proliferation, extracellular matrix remodelling, and regulation of gene expression via signalling pathways leading to tissue injury [8, 12]. Ang-II promotes expression of pro-inflammatory chemokines in the kidneys, heart, and vasculature to induce inflammation [13]. Several studies have characterized key inflammatory processes influenced by Ang-II on macrophages, dendritic cells, and mesangial cells resulting in mobilization and activation of cytokines, chemokines, and pro-inflammatory factors resulting in tissue damage and progressive organ failure [14]. Due to profound influence of Ang-II signalling pathways that are predominantly adverse when unmitigated, the potency of Ang-II is tightly regulated via proteolytic activities of enzymes to generate various angiotensin peptide fragments with physiological activities different from Ang-II [14] (Fig. 1a). ACE2 is an enzyme component of RAS, with proteolytic activities different from the canonical ACE. ACE2 is responsible for cleaving angiotensin I to Ang (1–9) and angiotensin-2 to Ang (1–7) peptides respectively (Fig. 1), of which the latter is a potent vasodilator [15, 16]. Several studies support a major role for Ang (1–7) in providing the counterbalance to the physiological effects of Ang-II [17,18,19]. Thus, the pro-inflammatory effects of ACE/Ang-II axis are balanced by activation of anti-inflammatory pathways by ACE2 and other systems.

除了血液动力学作用，Ang–II还具有显著的促炎症作用，促进活性氧（ROS）的产生，细胞增殖，细胞外间质重塑，以及通过信号通路调节基因表达导致组织损伤[8,12]。Ang– II 促进炎症趋化因数在肾脏、心脏和血管系统的表达以诱导炎症[13]。一些研究表明，Ang–II 影响巨噬细胞、

树突状细胞和系膜细胞的关键炎症过程，导致细胞因数、趋化因数和促炎因数的动员和启动，从而导致组织损伤和进行性器官衰竭[14]。由于Ang– II 信号转导途径的深刻影响，这些途径主要是逆转的，所以Ang– II 的效力是通过酶的蛋白水解活性来产生各种血管紧张素肽片段，其生理活性不同于Ang– II [14](图1a)。ACE2是 RAS 的一个酶组分，具有不同于正规 ACE 的蛋白水解活性。ACE2分别参与血管紧张素–I（angiotensin I，Ang)(1–9)和血管紧张素–II(angiotensin–II，Ang)(1–7)的分离(图1)，其中血管紧张素2是一种强有力的血管扩张剂[15,16]。一些研究支援血管紧张素(1–7)在提供抗衡Ang– II（17,18,19)的生理效应的主要作用。因此，ACE/Ang–II 轴的促炎作用是通过 ACE2和其他系统启动抗炎通路来平衡的。

ACE Insertion/Deletion (ID) Polymorphisms: Prevalence ACE

基因插入/缺失(ID)多态性: 患病率

Two recent publications reported that ACE insertion/deletion polymorphism correlated to infectivity and mortality associated with COVID-19 infections [7, 20]. In humans, the gene encoding ACE is located on chromosome 17 and exhibits an insertion/deletion polymorphism that is characterized by an insertion (allele I) or deletion (allele D) of a 287 base pair marker in intron 16 that results in three different genotypes, i.e. DD or II homozygotes or ID heterozygotes. It is reported that the deletion (D) allele occurs in 55% of the population and associated with increased ACE activity, implicating the presence of D allele with disease pathologies associated with RAS activity [21].

两个最近的出版物报导 ACE 插入/缺失多态性与COVID–19疾病感染的传染性和死亡率相关[7, 20]。在人类中，编码 ACE 的基因位于17号染色体，具有插入/缺失多态性，即内含子16中一个287个城基对标记的插入/缺失(等位基因I)或拥有属性(等位元基因 D)，导致产生3种不同的基因型，即 DD 或 II 纯合子或 ID 杂合子。据报导，缺失(D)等位基因发生在55% 的人口和增加 ACE 活性，提示 d 等位基因的存在与 RAS 活性相关的疾病病理[21]。

The Allele Frequency Database (ALFRED; https://alfred.med.yale.edu/alfred/index.asp; RRID:SCR_001730) was queried for frequency of rs4646994 representing ACE I/D polymorphism, one of the best studies of all ACE polymorphisms. The allelic frequencies of the insertion (I, +) and deletion (D, –) genotypes within various geographic regions from 349 population samples were obtained from ALFRED and are summarized in Table 1. Inclusion of data from all European studies demonstrated almost equal distribution of the ACE (I) or ACE (D) allele, with Italians, Ashkenazi Jews and Canarians demonstrating slightly higher prevalence compared with the population averages. In contrast to Europe, among the African population, the frequency of D allele was almost twice compared with the I allele among 2126 population samples with highest levels observed in Pygmies, Ethiopian Jews, Moroccan, Nigerian and Tunisian populations. These are consistent with other studies reporting significant increase in the frequency of deletion polymorphism of ACE observed in individuals of African descent and associated with disease pathology [22]. Specifically, a prevalence of the D allele of 60% has been reported in individuals of African descent [22]. In the USA, the non-Hispanic Black population has higher frequency of the D allele (Table 2) compared with non-Hispanic White and Mexican American population [23]. The frequency of the D allele was increased compared with the I allele within the Middle Eastern population with higher values observed in both Arab and Saudi Arabia sample populations. In contrast to Africa and Middle East, increased

frequency of the I allele was observed in sample populations from Asia (India, Pakistan Nepalese, Tajik regions and Sri Lanka), Oceania (New Zealand, Papua New Guinea and Micronesia), East Asia (China, Japan, Korea, Taiwan, Cambodia, Vietnam, Philippines and Malaysia) and South American countries.

等位元基因频率资料库(ALFRED; https://ALFRED.med.yale.edu/ALFRED/index.asp ; RRID: SCR _ 001730)查询了 rs4646994代表 ACE I/D 多态性的频率，这是所有 ACE 多态性研究中最好的一个。从349个群体样本中获得了插入(I，+)和缺失(D，–)基因型在不同地理区域的等位元基因频率，总结见表1。纳入所有欧洲研究的资料表明，ACE (I)或 ACE (D)等位基因的分布几乎相等，义大利人、德系犹太人和卡纳里亚印第安人的患病率略高于人口平均水准。在2126个人口样本中，D 等位元基因的频率几乎是 I 等位元基因频率的两倍，在俾格米人、衣索比亚犹太人、摩洛哥人、奈及利亚人和突尼斯人中观察到的 D 等位元基因频率最高。这些结果与其他研究报告的结果一致，即在非洲人后裔个体中观察到的 ACE 基因缺失多态性的频率显著增加，并与疾病病理学有关[22]。具体而言，在非洲人后裔中，D 等位基因的患病率率为60% [22]。在美国，非西班牙裔黑人人口有更高的 D等位元基因频率(表2)相比，非西班牙裔白人和墨西哥裔美国人口[23]。D 等位元基因频率在中东人群中比I等位元基因频率增加，在阿拉伯和沙乌地阿拉伯样本人群中观察到的数值更高。与非洲和中东不同，在亚洲(印度、巴基斯坦尼泊尔、塔吉克地区和斯里兰卡)、大洋洲(纽西兰、东南亚和密克罗尼西亚)、东亚(中国、日本、韩国、台湾、柬埔寨、越南、菲律宾和马来西亚)和南美国家的样本人群中观察到 I等位元基因频率增加。

Table 1 Prevalence of ACE insertion/deletion polymorphism: the Allele Frequency Database (ALFRED) was queried for identifying population frequency of the ACE insertion/deletion polymorphism among geographical locations. From a total of 349 population samples, the average frequencies of the insertion and deletion allele for ACE were calculated for the different geographical locations. The table provides the population sample size and frequency (italicized) and the breakdown of the frequency of the insertion and deletion allele within specific ethnic groups of interest within the population

表1 ACE 插入/缺失多态性的普遍性: 为了确定不同地理位置间 ACE 插入/缺失多态性的人群频率，我们对等位元基因频率资料库(Allele Frequency Database, ALFRED)进行了查询。从349个人群样本中，计算了 ACE 基因插入和缺失等位基因在不同地理位置的平均频率。该表提供了人口抽样数量和频率(斜体)，以及人口中特定种族群体内插入和删除等位元基因频率的细目

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		样本大小 (N)	插入	缺失
欧洲		*16,220*	*0.412*	*0.588*

		样本大小 (N)	插入	缺失
	阿巴齐安人	24	0.000	1.000
	加纳里安	1358	0.375	0.625
	英国人	924	0.454	0.546
	法国人	2234	0.423	0.578
	爱尔兰人	226	0.429	0.571
	义大利人	222	0.342	0.658
	犹太人, 阿什凯纳齐	154	0.340	0.660
非洲		*2126*	*0.340*	*0.660*
	俾格米人	68	0.221	0.779
	犹太人, 埃塞俄比亚	64	0.203	0.797
	摩洛哥人	106	0.292	0.708
	尼日利亚人	22	0.273	0.727
	突尼斯人	200	0.325	0.675
中东		*1714*	*0.360*	*0.640*
	阿拉伯人	100	0.290	0.710
	沙特人	540	0.275	0.725
亚洲		*7380*	*0.585*	*0.414*
大洋洲		*1444*	*0.684*	*0.315*
东亚		*3182*	*0.627*	*0.372*
南美		*2458*	*0.706*	*0.293*

Table 2 ACE polymorphism allele and genotype frequencies: the prevalence of 289-bp Alu insertion/deletion in intron 16 of ACE gene corresponding to rs4646994 within the non-Hispanic White and non-Hispanic Black population is described. (Information modified from source provided by Office of Science (OS), Office of Genomics and Precision Public Health, CDC 2009; complete data is available at https://www.cdc.gov/genomics/population/genvar/frequencies/ace.htm)

表2 ACE 多态性等位元基因和基因型频率: 在非西班牙裔白人和非西班牙裔黑人人口中，ACE 基因内含子16中与 rs4646994相对应的289–bp Alu 插入/缺失的流行率被描述。(资讯修改自2009年疾病预防控制中心基因组学与精确公共卫生办公室科学办公室(OS)提供; 完整资料查询网址 https://www.cdc.gov/genomics/population/genvar/frequencies/ace.htm)

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基因变异	民族/种族	等位基因%		等位基因% (95% 置信区间)			卡方检验p值	HW *p* 值
		D	I	DD	DI	II		
rs4646994	非-西班牙裔 白人	54.6	45.4	28.8 (25.9,31.8)	51.6 (47.8,55.3)	19.6 (17.7, 21.8)	< 0.001	0.11
	非-西班牙裔 黑人	58.7	41.3	33.8 (31.5,36.3)	49.8 (47.3,52.2)	16.4 (14.6,18.5)		0.1

ACE Deletion (D) Polymorphism and Disease—Increased Susceptibility and Severity to Co-morbidities Associated with COVID-19

ACE 缺失(D)基因多态性与疾病—与COVID-19疾病相关的合并症易感性和严重程度增加

Although the ACE I/D polymorphism is located in a non-coding region, its presence is directly linked to regulation of renin-angiotensin system and associated pathological conditions. A positive association between D allele and high blood pressure, atherosclerosis, coronary artery disease, stroke, diabetic nephropathy and Alzheimer's disease has been extensively reviewed [24]. The molecular underpinning of these diseases is multi-factorial and complex, and the presence of the ACE deletion polymorphism may contribute to influence disease pathology. Indeed, to date, there is distinct lack of consensus studies linking the presence of ACE deletion polymorphism to disease causality. Nevertheless, the increase in levels of ACE in individuals with the ID and DD genotypes and potential augmentation of the RAS system and associated signalling cascades can influence pathways to influence disease pathology [25] (Fig. 1b). Indeed, increased levels of ACE and Ang-II have been implicated in the pathophysiology of lung (pulmonary hypertension, pulmonary fibrosis, acute lung injury and acute respiratory distress syndrome [26, 27]) and kidney disease (chronic kidney disease, diabetic nephropathy [28, 29]). In the African American population, the deletion polymorphism is associated with increase in systolic blood pressure, hypertension and altered vascular reactivity with potential impact on cardiovascular disease [30,31,32].

尽管 ACE I/D 多态位于非编码区，但它的存在与RAS和相关病理状态的调节直接相关。D 等位基因与高血压、动脉粥样硬化、冠状动脉疾病、中风、糖尿病肾病和阿尔茨海默氏病之间的正相关已经得到广泛的研究[24]。这些疾病的分子基础是多因素和复杂的，ACE 缺失多态性的存在可能有助于影响疾病的病理。事实上，到目前为止，明显缺乏共识的研究，将 ACE 缺失多态性的存在与疾病的因果关系联系起来。尽管如此，在 ID 和 DD 基因型个体中 ACE 水准的增加和 RAS

系统的潜在增强以及相关的信号通路可以影响疾病病理学的通路[25] (图 1b)。事实上，ACE 和 Ang–II 水准的升高与肺部病理生理学(肺部高压、肺纤维化、急性肺损伤和急性呼吸窘迫症候群[26, 27])和肾脏疾病(慢性肾脏疾病、糖尿病肾病疾病[28, 29])有关。在非洲裔美国人中，缺失多态性与收缩压升高、高血压和血管反应性改变有关，对心血管疾病有潜在影响[30,31,32]。

A subset of individuals with a positive diagnosis of COVID-19 infection have rapid progression of lung dysfunction leading to acute respiratory distress with potential need for ventilatory support [2, 3]. Presence of ACE insertion/deletion (I/D) polymorphism is associated with susceptibility and is an independent risk factor for mortality in patients with acute respiratory distress syndrome (ARDS) [33, 34]. Of the three ACE polymorphisms, there is positive association with frequency of the DD allele and incidence of ARDS, increased fatality and a prognostic factor of outcomes [35,36,37]. Further, the DD genotype is usually associated with higher ACE levels relative to other genotypes and with increased mortality in acute lung injury (ALI)/ARDS patients [38, 39]. Elevated levels of ACE have been observed in the bronchoalveolar fluid of individuals with ARDS [28]. Although decreases in circulating ACE have been reported in ARDS patients [40], this might be a consequence of the progressive damage to lung tissue as increased levels of ACE are evident in the bronchoalveolar fluids of individual with ARDS [40]. The positive relationship between DD genotype and ALI/ARDS and the corresponding increase in ACE levels suggest the potential involvement of increased Ang-II in the etiopathology of ARDS. During the avian (H7N9) flu infections, approximately 70% of patients developed ARDS [41]. In a subset of infected patients, increase in plasma Ang-II levels was linked to severity and fatal outcomes [41].

一组确诊为COVID–19感染的患者肺部功能障碍进展迅速，导致急性呼吸窘迫，可能需要呼吸支持[2, 3]。ACE 插入/缺失(I/D)多态性的存在与急性呼吸窘迫症候群易感性有关，是导致急性呼吸道窘迫综合症（ARDS，下文用ARDS替代）患者死亡的独立危险因素。[33, 34].在三个 ACE 基因多态性中，DD 等位元基因频率与 ARDS 发生率、病死率和预后因素呈正相关[35,36,37]。此外，DD 基因型通常与其他基因型相对较高的 ACE 水准有关，并且与急性肺损伤(ALI)/ARDS 患者死亡率增加有关[38, 39]。在 ARDS 患者的支气管肺泡液中观察到 ACE 水准升高[28]。虽然在 ARDS 患者中已有回圈 ACE 下降的报导[40],，但这可能是由于 ARDS 患者的支气管肺泡液中 ACE 水准明显升高导致肺组织进行性损害的结果[40]。DD 基因型与 ALI/ARDS 呈正相关，ACE 水准相应升高，提示 Ang–II 水准升高可能参与 ARDS 的发病机制。在禽流感(H7N9)感染期间，大约70% 的患者出现了 ARDS。在一部分感染患者中，血浆 Ang–II 水准的升高与严重程度和致命后果有关[41]。

Within the COVID-19-infected population, there is increased incidence of kidney injury associated with higher mortality rates [42, 43]. Chronic kidney disease (CKD) is associated with severity of COVID-19 infection [44]. Interestingly, both ACE and ACE2 expressions in the kidneys are predominant in the proximal tubules with minor expression in the glomerular apparatus [45]. The balance between Ang-II and Ang (1–7) affects renal RAS to maintain balance of kidney functions; imbalance of the ratio results in kidney disease [46,47,48]. Chronic kidney disease is characterized by decreases in cardiac and renal ACE2 in human [49]. Diabetic nephropathy (a CKD) is characterized by decrease in ACE2, increased ACE and Ang-II-mediated tubular and glomerular damage as a result of renal RAS activation [28, 29]. Based on these studies, the ability of COVID-19 to bind and decrease ACE2 in target tissues is most likely responsible for the observed increase in blood urea nitrogen, proteinuria and hematuria associated with kidney damage [49]. Thus, COVID-19-associated decrease in ACE2 most likely results in disruption of

the ACE/ACE2 balance in the kidney leading to sustained activation of ACE and Ang-II activities and kidney damage. ACE insertion/deletion polymorphism is also associated with diabetic kidney disease, the frequency of DD and ID genotype distribution being higher compared with non-diabetic kidney disease cohorts, leading to functional decline [50, 51]. The above observations suggest that presence of the DD genotype of ACE in patients with COVID-19 infection may be associated with severe respiratory distress compared with the other genotypes.

在COVID–19感染人群中，与较高死亡率相关的肾损伤发生率增加[42, 43]。慢性肾脏疾病(CKD)与COVID–19疾病感染的严重程度相关。有趣的是，ACE 和 ACE2在肾脏中的表达在近端肾小管中占主导地位，而在肾小球器官中的表达较少[45]。Ang– II 和Ang(1–7)之间的平衡影响肾脏 RAS 以维持肾脏功能的平衡，比例导致肾脏疾病[46,47,48]。慢性肾病以人的心肾ACE2下降为特征[49]。糖尿病肾病(CKD)的特点是ACE2减少，ACE和Ang–II介导的肾小管和肾小球损伤增加，这是肾脏RAS启动的结果[28, 29]。基于这些研究，COVID–19结合和降低靶组织中ACE2的能力很可能是导致血尿素氮、蛋白尿和血尿升高并伴有肾损伤的原因[49]。因此，与 covid–19相关的 ACE2减少最有可能导致肾脏中 ACE/ACE2平衡的破坏，从而导致 ACE 和 Ang–II 活性的持续启动和肾脏损伤。ACE 插入/缺失多态性也与糖尿病肾病相关，DD 和 ID 基因型分布频率高于非糖尿病肾病组，导致功能下降[50, 51]。上述观察表明，与其他基因型相比，COVID–19疾病感染患者中存在 DD 型 ACE 可能与严重的呼吸窘迫有关。

Multiple studies have reported on the prevalence of ACE I/D polymorphism, specifically the ID and DD polymorphism in increasing levels of ACE and Ang-II, which could in part influence susceptibility to underlying pathologies considered high risk for COVID-19 infections, progressive organ dysfunction and poor outcomes. Thus, presence of ID and DD polymorphism by itself is a potential underlying risk factor associated with severity and outcomes in individuals with positive diagnosis of COVID-19 infection [20, 21].

多项研究已报导 ACE I/D 多态性的流行，特别是在 ACE 和 Ang–II 水准增加中的 ID 和 DD 多态性，这可能一定程度上影响潜在疾病的易感性，这些疾病被认为是COVID–19疾病感染、进行性器官功能障碍和不良结果的高危因素。因此，在COVID–19阳性诊断患者中，ID和DD多态性本身就是与病情严重程度和预后相关的潜在潜在危险因素[20, 21]。

ACE–2 Inhibition by COVID–19: Increased RAS Activity

COVID-19抑制ACE-2: 增加 RAS 活性

The proteolytic cleavage of Ang-II by ACE2 to generate Ang (1–7) represents a major event leading to the physiological inactivation of Ang-II function. Thus, in patients with active COVID-19 infections, decrease in ACE2 expression/activity should most likely lead to sustained ACE-mediated generation of Ang-II and downstream signalling deleterious to organ functions including that of lung, kidney and heart [52]. Although the status of circulating and lung ACE levels in COVID-19 patients is unclear, the ability of SARS-CoV-2 binding specifically to ACE2 decreases its expression and activity suggesting upregulation of ACE/Ang-II-mediated activities. This is consistent with the observation that knockdown of ACE2 is associated with severe ARDS in multiple rodent models compared with corresponding wild-type controls [18].

Loss of ACE2 expression in mutant mice is associated with worse lung function and characterized by increases in vascular permeability, lung oedema and neutrophil accumulation [18]. Interestingly, reduced plasma levels of ACE2 are also observed within populations of African descent including African Americans, specifically in individuals with pre-hypertensive status, diabetes and renal disease [53, 54]. Administration of a catalytically active recombinant ACE2 protein improved symptoms of acute lung injury in ACE2 knockout and wild-type mice [55]. In a pilot clinical investigation, administration of recombinant human ACE2 (APN311) in patients with acute respiratory distress was associated with rapid decrease in Ang-II level and did not significantly influence oxygenation indices in the treated population compared with placebo-controlled group [56]. The recombinant human ACE2 is undergoing renewed clinical testing in the COVID-19 patient population to investigate clinical outcomes [52].

血管紧张素 II(Ang–II)的蛋白水解切割产生Ang（1–7）是导致Ang–II 功能失活的一个重要事件。因此，在活性COVID–19疾病感染的患者中，ACE2表达/活性的降低很可能导致持续的ACE介导的Ang–II和下游信号通路的产生，对包括肺、肾和心脏在内的器官功能有害[52]。虽然回圈和肺 ACE 水准在COVID–19患者中的状况尚不清楚，但 SARS–CoV–2特异性结合 ACE2的能力降低了其表达和活性，提示 ACE/ Ang–II 介导的活性上调。这与多种啮齿动物模型与相应的野生型对照组相比，ACE2下调与严重 急性呼吸窘迫综合征相关的观察结果是一致的[18]。突变小鼠ACE2表达缺失与肺功能恶化、拥有属性通透性增加、肺水肿和中性粒细胞积聚有关[18]。有趣的是，在包括非裔美国人在内的非洲裔人群中，特别是在高血压前期、糖尿病和肾病患者中，血浆 ACE2水准也有所下降。给予具有催化活性的重组 ACE2蛋白可改善 ACE2基因敲除小鼠和野生型小鼠的急性肺损伤症状[55]。在一个初步的临床研究中，给予重组人血管紧张素转换酶 2(APN311)治疗急性呼吸窘迫患者，Ang–II水准迅速下降，与安慰剂对照组相比，治疗组人群的氧合指数没有显著影响[56]。重组人血管紧张素转换酶2正在COVID–19疾病患者群体中重新进行临床试验，以研究临床效果[52]。

ACE2 inhibition by COVID-19 Plus ACE D Polymorphism: Synergized RAS—Rationale for Use of ACE-I and ARBs in Clinical Management

COVID-19和ACE D 多态性对ACE2的抑制作用: 协同的RAS-临床管理中使用ACE-I和ARBs的理论基础

SARS-CoV-2 binding to ACE2 results in reduction of protein expression, activity and ability to generate anti-inflammatory signalling, all of which contribute to a pro-inflammatory phenotype due to presence of ACE activity and Ang-II signalling (Fig. 1c). Presence of ACE D polymorphism increases ACE levels and Ang-II leading to pro-inflammatory phenotype and is associated with disease susceptibilities considered high risk for COVID-19 infections. Recently, it was proposed that reduced plasma levels of ACE2 in individuals of African descent most likely lowers potential for COVID-19 infection [57]; the overall outcomes in individuals with presence of ACE deletion polymorphism after infection with COVID-19 most likely leads to exacerbation of comorbidities and overall deleterious outcomes. Based on the described biological consequence of COVID-19 infections on the RAS system, treatment with ACE-I and ARBs should be associated with improved outcomes within the overall COVID-19 patient cohorts. Indeed, several meta-analyses provide preliminary support for the potential benefits of the use of ACE-I/ARBSs in management of COVID-19 infections.

SARS-CoV-2与 ACE2结合导致蛋白质表达、活性和产生抗炎信号的能力下降，所有这些因 ACE 活性和血管紧张素转换酶 II(Ang-II)信号的存在而促进炎症表型的产生(图1c)。ACE D多态性的存在增加 ACE 水准和Ang-II，导致促炎症表型，并与疾病易感性被认为是COVID-19疾病感染的高风险相关。最近，有人提出，非洲血统个体血浆 ACE2水准的降低很可能降低了COVID-19疾病感染的可能性[57]; 在感染COVID-19疾病后存在 ACE 缺失多态性的个体中，总体结果最有可能导致并发症和总体有害结果的加重。基于所描述的COVID-19疾病感染对 RAS 系统的生物学后果，ACE-I和ARBs 治疗应该与整个COVID-19疾病患者群体的改善结果相关联。事实上，一些荟萃分析为使用ACE-I/ARBSs 治疗COVID-19疾病感染的潜在益处提供了初步支持。

In a multicenter study of 1128 adult patients with hypertension with positive COVID-19 diagnosis, in-patient use of ACE-I/ARBS was associated with reduced risk of mortality from all causes when compared with patients not treated with the medications [58]. Recent publications further highlight the use of ACE-I and ARBs in providing cardiovascular and renal benefits to patients with COVID-19 diagnosis [59, 60]. In a meta-analysis, patients treated with ACE-I/ARBSS had 44% reduction in odds of developing severe disease and death compared with patients not treated with ACE-I/ARBSs [61]. These studies provide rationale for investigation into the utility of ACE-I/ARBSs in the ethnic population with known prevalence of ACE deletion polymorphisms in an effort to mitigate severity and improve outcomes in response to COVID-19 infections.

在一项针对1128名COVID–19阳性的成年高血压患者的多中心研究中，与未接受药物治疗的患者相比，住院患者使用ACE–I/ARBS与各种原因的死亡风险降低有关[58]。最近的出版物进一步强调使用ACE–I和ARBs对COVID–19确诊患者的心血管和肾脏有益[59, 60]。在一项荟萃分析中，接受 ACE–I/ARBS治疗的患者与未接受ACE–I/ARBS治疗的患者相比，发生严重疾病和死亡的几率降低了44% [61]。这些研究为调查ACE缺失多态性普遍存在的少数民族人群中ACE– i / ARBSs的效用，以减轻严重程度和改善COVID–19感染的结果提供了理论基础。

Use of ACE-I/ARBSs in Ethnic Population with Increased Prevalence of ACE D Polymorphism for Management of COVID-19

ACE-I/ARBs 在 ACE D基因多态性增高的少数民族人群中应用于COVID-19疾病管理

ACE is a multi-functional, relatively non-specific peptidase enzyme with a wide range of substrate specificities that impact physiological pathways in influencing blood pressure, haematopoiesis, hormone regulation, renal function and immune responses. The specificity of hypertension and cardiovascular disease as underlying causes for severity of COVID-19 infection, the inherent role of ACE-mediated generation of Ang-II and downstream signalling to potentially exacerbate inflammation and organ damage along with genotypic impact on ACE status provide compelling support of the use of ACE-I and ARBs in the clinical management of patient with positive diagnosis of COVID-19.

ACE 是一种多功能、相对非特异性的肽酶，具有多种底物特异性，在影响血压、造血、激素调节、肾功能和免疫反应等方面影响生理途径。高血压和心血管疾病的特异性是COVID-19疾病感染严重程度的根本原因，ACE 介导的Ang-II和下游信号的内在作用可能加剧炎症和器官损伤，以

及对 ACE 状态的基因型影响，都为在临床上使用ACE-I和ARBs治疗COVID-19阳性患者提供了有力的支持。

The biological impact of the presence of deletion polymorphism of ACE in individuals with COVID-19 infection provides a significant rationale for serious consideration of short-term use of ACE-I and/or ARBs in patients without underlying issues with blood pressure or cardiovascular disorder. The guidance statement issued by the Heart Failure Society of America (HFSA), the American College of Cardiology (ACC) and American Heart Associated (AHA) states that in the absence of favourable or detrimental effects of ACE-I and ARBs in the COVID-19 setting, the recommendation is to not arbitrarily or pre-emptively discontinue these agents in patients currently on the medication as standard of care (acc.org). Indeed, both ACE-I and ARBs have been extensively used in conditions ranging from hypertension, congestive heart failure, prevention of kidney failure and other indications. Both classes of drugs have extensive use history, understanding of safety, tolerability, efficacy, adverse events profile and drug interactions. The significant genetic, scientific and clinical data supporting a potential role for increased ACE levels and associated Ang-II effect in target organs provides compelling argument for use of ACE-I and ARBs in the clinical management of patients with COVID-19 infections to improve outcomes. High salt sensitivity–associated low plasma renin activities are responsible for the attenuated blood pressure–lowering response of ACE-I in the African American population [62]. However, this particular phenomenon might be of potential advantage in dosing and management of severity of COVID-19-associated morbidities in African American and other ethnic populations with ACE deletion polymorphism.

COVID-19感染个体中ACE缺失多态性的生物学影响，为没有潜在血压或心血管疾病问题的患者考虑短期使用ACE- i和/或ARBs提供了重要依据。。美国心力衰竭协会(HFSA)、美国美国心脏病学学院协会(ACC)和美国心脏协会(AHA)发布的指导声明指出，在COVID-19疾病环境中，如果没有ACE-I和ARBs 的有利或不利影响，建议不要武断或率先停止使用这些作为标准治疗的药物(acc.org)。事实上，ACE-I和ARBs都被广泛应用于高血压、心衰竭、预防肾功能衰竭和其他适应症。这两类药物都有广泛的使用历史，并了解其安全性，耐受性，疗效，不良事件概况和药物相互作用。重要的遗传学、科学和临床资料支援 ACE 水准升高的潜在作用以及靶器官中相关的 Ang-II 效应，为在COVID-19感染患者的临床管理中使用ACE-I和ARBs 改善预后提供了令人信服的论据。高盐敏感性相关的低血浆肾素活性是造成非裔美国人ACE-I 降低血压反应减弱的原因[62]。然而，该特殊现象可能存在于非裔美国人和其他具有ACE缺失多态性的种族人群中，对COVID-19相关病症的严重程度的剂量和管理具有潜在优势。

In summary, this study describes the biological relevance of genetic polymorphism of ACE deletion with higher prevalence in certain ethnic populations including African Americans in context of COVID-19 infection and rationale for the use of ACE-I/ARBSs for therapeutic management of severity of morbidity and improving outcomes associated with COVID-19.

综上所述，本研究描述了 ACE 缺失基因多态性与某些种族人群包括非裔美国人在COVID–19疾病感染背景下较高患病率的生物学相关性，以及使用 ACE–I/ARBSs 治疗疾病严重程度和改善与改善COVID–19相关预后的原理。

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